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(54) Method for the preparation and examination of multiple samples for microscopical and scientific study and analysis

(57) A method and apparatus for examination of a series of samples in which the samples are deposited in succession upon a continuous plastic support and treated to secure, process, protect and preserve them for examination, especially by microscopical study and analysis. Data relevant to the samples is recorded on the plastic support in register with the samples, and further data from the examination of the samples can be recorded on the same support or on a separate record so that data for each sample can be correlated and used for further study or evaluation of the samples. Readily applicable to biological samples, especially those requiring mass study for diagnostic purposes (e.g. cervical smears). Obviates use of bulky glass slides, and facilitates study of large numbers of samples and the use of computer aids for improving speed of evaluating and re-checking samples.

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## SPECIFICATION

## Method for the preparation and examination of multiple samples for microscopical and scientific study and analysis

This invention relates to a method for the preparation and examination of multiple samples for microscopical and scientific study and analysis, and more particularly to a method for the examination of large numbers of scientific samples, of example biological and diagnostic samples.

It is well known, for example, to prepare and examine large numbers of samples of biological material to look for predetermined characteristics (other faults or abnormalities) and this process including "screening" is commonly applied to the routine examination of biological specimens for microscopical study and analysis for such purposes as checking for cancerous or pre-cancerous conditions in, for example, tests such as tissue samples or smears, for example cervical smears. It is also necessary in most cases for the samples to be stored for some time after examination, so that they can if required be re-examined at a later date.

In dealing with such multiple samples, however, there is the especial problem of doing this speedily and reliably, as the usual samples, for example biological samples, have to be carefully prepared before they can be examined, and this almost inevitably requires their preparation as on individual glass supports (for example glass microscope slides).

Unfortunately, such glass supports are weighty, fragile, inflexible and hazardous, requiring the addition of a glass cover-slip once the sample has been applied and processed. This procedure does not lend itself readily to the rapid examination of large numbers of samples, or to the introduction of automated processing and analysing instruments. This is partly because of the sheer difficulty of preparing and handling specimens on individual glass supports/cover-slips and partly because the very large amounts of glass used has to be transported and stored, presenting problems of fragility, excessive weight and hazards.

There is a great need for rapid examination of large numbers of samples in research, screening, diagnosis, teaching, prevention of disease and for general microscopic study. For example, cervical cancer screening, efficacy testing of novel drugs or chemical/physical industrial reagents and products and the routine histological analysis of tissue samples for the study and diagnosis of disease. Increasing the volumes of tests and consequently the number of individual glass supports produces a higher probability of error and difficulties of storage and retrieval of glass-supported (e.g. glass slide) collections. This is, in part, ham-

pering the adoption of tests and testing systems on as wide a scale as is desirable.

We have now discovered that these difficulties can be overcome by using certain sheet plastic materials in place of the conventional glass supports.

Thus according to our invention we provide a method for the examination of a series of samples which comprises depositing the said samples in succession upon a continuous plastic support, and treating the said samples upon the said plastic support

- (i) to secure the said samples to the said plastic support,
- 80 (ii) to process the said samples appropriately for examination, and
- (iii) to protect and preserve the said samples.

The samples may be, for example, biological samples but alternatively may be any other form of samples which may be suited or required for microscopical examination. The samples may be in any convenient form for examination, for example microtome sections.

90 The procedure of our invention is especially valuable because it can be used to provide more than just the facility for rapid examination but also the facility for recording the data relevant to each sample, for allowing the results to be scanned quickly, and for searches to be made for identification and easy access to those samples which meet any specified criteria. The invention is thus of especial value to those users preparing large numbers of samples for detailed microscopical study and investigation.

Accordingly, the present invention also comprises methods and apparatus for the microscopical examination of a series of samples, for example biological samples, characterised in that the samples are deposited for examination as a series in succession on a continuous plastic support and data relevant to the said samples is recorded on the said support in 100 register with the said samples.

Thus according to a further feature of our invention we provide a method for the examination of a series of samples which comprises depositing the said samples in succession upon a continuous plastic support, and treating the said samples upon the said plastic support in the manner specified above, and also

- (a) marking the said plastic support with indicia providing characteristic unique data for each sample and correlated with it,
- (b) passing the said plastic support, with the samples and indicia thereon, through apparatus which is adapted to examine and analyse 115 the samples, and
- (c) recording the data of the examination results (from b) and correlating it with the indicia (a).

As a further step, there can then be added 130 that of:-

(d) processing the correlated data (from a and c) to give an output of the relationship between the examination data and the characterising data of samples in selected report 5 form.

According to our invention we also provide apparatus for the examination of a sequential series of samples which comprises:-

A. means for depositing the said samples 10 in succession upon a continuous plastic support,

B. means for treating the said samples upon the plastic support to prepare the said samples appropriately for microscopical study 15 and analysis,

C. means for securing the said samples to the said plastic support,

D. means for protecting and preserving the said samples upon the said plastic support,

20 E. means for marking the said plastic support with indicia providing data characterising each sample and correlated with each sample,

F. means for enabling the said plastic support, with the samples and indicia thereon, to 25 be passed through apparatus which is adapted to allow examination of the samples, especially for microscopical study and analysis,

G. means for recording the data of the examination results (from F) and correlating them 30 with the indicia (from E),

H. means for processing and storing the correlated data (from G) to enable an output of the relationship of examination data to samples to be obtained in selected report 35 form when required.

The apparatus according to the invention may comprise all the features indicated above or any desired combinations of them (or even individual ones) adapted to be combined to 40 assemble an apparatus suitable for putting the invention into practice.

Such apparatus may require to be "customised" i.e. adapted from the conventionally available forms of equipment to make it more 45 suited for use in carrying out the procedures or combinations of procedures of the invention.

The materials for the continuous plastic support (which may be referred to conveniently 50 as a plastic film strip) may be any which are sufficiently durable and stable to survive the processes of treatment and examination to which they may be submitted or may potentially be required to be submitted, either in 55 preparation or use. For example,

(1) they should be resistant to water and any organic solvents or reagents used, so that they do not distort or soften;

(2) they should not contain components 60 which can damage the samples carried nor them out retain reagents (coloured or otherwise) that may impair the sample for examination or interpretation;

(3) they should not readily absorb water, 65 chemicals or reagents in a comparable manner

to the samples they may carry;

(4) they should be flexible enough to facilitate storage, winding and running through apparatus, etc., without embrittlement, wear, 70 tearing or creasing;

(5) they should not be biodegradable or subject to an alteration in optical quality with the passage of time, and should be stable to variations in ambient temperature;

75 (6) they should be strong, durable and printable, and preferably have a melting point above 200 degrees C.

Such exhaustive criteria are essential for the best operation of the processes and procedures indicated above, so it is preferred that the plastic support possesses as many of them as can be economically or practicably achieved.

Optically clear materials suitable for the purposes of the present invention include polyester and polypropylene films, of which polyester is preferred as more suitable.

The thickness of the plastic support material, and its other dimensions, will depend to 90 some extent upon the particular apparatus and examination procedures to be used, but the following are useful guides to what, in general, these may most conveniently be (but are not necessarily limited to):-

95 (a) the thickness should be less than 175 $\mu$ m and optimally about 100 $\mu$ m.  
(b) the width should be less than 100mm, with optimum dimensions of 26mm, 38mm or 51mm, depending upon the specific application intended.

100 There is no operational limit on overall length, which may range from single metres to tens of metres, or even longer, so that many glass-support-equivalent lengths may be accommodated.

105 The treatment procedures (i) to (iii) above may be any conventional ones known in the art. For example, in the preparation of tissues for microscopical study there may be used material infiltrated with paraffin wax, material frozen for sectioning using cryostat or Peltier effect devices or utilising coolant liquids or gases, untreated ambient temperature sections, smears or solutions containing any biological material.

110 The treatment of the continuous plastic support material to give it its ability to take up or hold the samples, for example biological samples, may be any conventional method known in the art, for example reagents and/or coatings to modify the surface so as to act as an intermediate "subbing" layer to stick to the surface and to the sample, but in particular may be a treatment of the plastic support with poly-L-lysine using a predeposition procedure.

115 The indicia providing characterising data may be any conventional ones and may take any desired form which can be imposed on or in 120 the plastic support and can be read by an

appropriate reader or sensor instrument. They should be of such form that they can survive the various treatment stages through which the samples have to pass, and also survive 5 storage, without the recorded indicia becoming debased and difficult to decipher or read again. Especially they may be optical, mechanical or magnetic indicia, or any combination of these, and application of them to the plastic 10 support may be by conventional processes that are known in the art.

The means for recording results of examination, especially microscopical study and analysis, (i.e. examination data) on to the plastic 15 support in step (c) above may be such as to record on to the plastic support itself, in register with the characterising data.

Alternatively, the examination data may be recorded on to a separate record which can 20 be read in conjunction with the data on the original plastic support and the two sets of data can then be correlated. This can be done for example by feeding the examination data into a customised computer database and 25 then reading this in conjunction with the original sample-carrying plastic support or a second database incorporating its data. The data can readily be correlated by computer processing to produce any desired output. For 30 example, the plastic support itself may be manipulated to give access to samples on it having any desired property or identity, or the data can be interpreted or analysed to provide a display or print-out of any desired data in 35 any desired format. The data may even be processed to produce a fresh database, optionally with provision for enhancement by addition of results of a subsequent further examination to augment the store of information 40 relating to the samples.

The nature, form & other characteristic of the biological samples which may be dealt with by the method of the present invention include any convenient or accessible form of 45 sample material, for example tissue samples, blood or other body fluid samples, including cervical smears, histological preparations of botanical or mammalian tissues, blood smears for diagnostic or pathological study, and 50 teaching materials - indeed, for example, any biological material. These may be kept in treated or untreated form, or re-treated, as required.

The procedures and apparatus of the 55 present invention may be used for the examination and study of any other samples, whether of biological nature or non-biological nature, which are susceptible to being carried upon the plastic support and examined upon it, in a 60 manner analogous to that described in more detail for biological samples.

The protection and/or preservation of biological samples when carried on the support may be any of the conventional ones known 65 in the art, for example treating them with

coatings or mountants, which may conveniently be applied by aerosol spray techniques, and sealing them in with a coating of a plastic film, for example a pre-coated adhesive self-sealing film, to seal in and protect the sample and indicia.

The prior treatment of the sample, treatment of the sample after deposition on the support, and the procedures and the materials 75 which may be used (e.g. preservative compositions or formulations and ingredients for these) are those known for the purpose and conventionally used and available.

The invention offers the advantages of 80 handing large numbers of samples in a speedy fashion, and also permits a degree of computer intervention (i.e. recording and processing of data by computer) that would be totally impracticable with the conventional glass supports.

#### CLAIMS

1. Method for the examination of a series of samples which comprises depositing the 90 said samples in succession upon a continuous plastic support, and treating the said samples upon the said plastic support

(i) to secure the said samples to the said support,  
95 (ii) to process the said samples appropriately for examination, and  
(iii) to protect and preserve the said samples.

2. Method for the examination of a series 100 of samples, as claimed in Claim 1 wherein the samples are deposited for examination as a series in succession on a continuous plastic support and data relevant to the said samples is recorded on the said plastic support in 105 register with the said samples.

3. Method for the examination of a series of samples, as claimed in Claim 1 or Claim 2 which comprises depositing the said samples in succession upon a continuous plastic support, and treating the said samples upon the 110 said plastic support in the manner specified above, and also

(a) marking the said plastic support with indicia providing characteristic unique data for 115 each sample and correlated with it,  
(b) passing the said plastic support, with the samples and indicia thereon, through apparatus which is adapted to examine and analyse the samples, and

120 (c) recording the data of the examination results (from b) and correlating it with the indicia (a).

4. Method for the examination of a series of samples, as claimed in Claim 3 wherein the 125 correlated data (from a and c) is processed to give an output of the relationship between the examination data and the characterising data of samples in selected report form.

5. Method for the examination as a sequential series of samples as claimed in any

one of Claims 1 to 4 wherein the materials for the plastic support is selected so as to be sufficiently durable and stable to survive the processes of treatment and examination to 5 which they may be submitted.

6. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 5 wherein the continuous plastic support is made of an optically clear 10 material.

7. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 6 wherein the continuous plastic support is made of polyester.

15 8. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 7 wherein the continuous plastic support has a thickness less than 175um, and preferably about 100um.

20 9. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 8 wherein the continuous plastic support material is treated to give it the ability to take up or hold the samples, for 25 example biological samples.

10. Method for the examination of a sequential series of samples as claimed in Claim 9 wherein the treatment of the plastic support is with poly-Lysine using a pre-deposition 30 procedure.

11. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 10 wherein the indicia providing characterising data is of such form 35 that they can survive the various treatment stages through which the samples have to pass, and also survive storage, without the recorded indicia becoming debased and difficult to decipher or read again.

40 12. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 11 wherein examination data is recorded for correlation with the samples on the continuous plastic support.

45 13. Method for the examination of a sequential series of samples as claimed in Claim 12 wherein the examination data is recorded on to the continuous plastic support itself, in register with the characterising data.

50 14. Method for the examination of a sequential series of samples as claimed in Claim 12 wherein the examination data is recorded on to a separate record which can be read in conjunction with the data on the original plastic support and the two sets of data can then 55 be correlated.

15. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 14 wherein the plastic 60 support itself is manipulated to give access to samples on it having any desired property or identity or the data is interpreted or analysed to provide a display or print-out of any desired data in any desired format.

65 16. Method for the examination of a sequential series of samples as claimed in Claim 15 wherein the data is processed to produce a fresh database, optionally possibly with provision for enhancement by addition of results 70 of a subsequent further examination to augment the store of information relating to the samples.

17. Method for the examination of a series of samples, as claimed in any one of Claims 1 to 16 wherein the samples are biological samples.

18. Method for the examination of a sequential series of samples as claimed in Claim 17 wherein the biological samples are tissue 75 samples, blood or other body fluid samples.

19. Method for the examination of a sequential series of samples as claimed in Claim 18 wherein the samples are cervical smears, histological preparations of botanical or mammalian tissues, or blood smears, for diagnostic or pathological study.

20. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 19 wherein the samples 80 are treated with a coating of a plastic film, for example a pre-coated adhesive self-sealing film, to seal in and protect the sample and/or indicia.

21. Method for the examination of a sequential series of samples as claimed in any one of Claims 1 to 20 wherein the examination is by microscopical study and analysis.

22. Method for the examination of a sequential series of samples substantially as described.

23. Apparatus for the examination of a sequential series of samples by a method claimed in any one of Claims 1 to 22.

24. Apparatus for the examination of a sequential series of samples which comprises:-

A. means for depositing the said samples in succession upon a continuous plastic support,

B. means for treating the said samples upon the plastic support to prepare the said samples appropriately for microscopical study and analysis,

C. means for securing the said samples to the said plastic support,

105 D. means for protecting and preserving the said samples upon the said plastic support,

E. means for marking the said plastic support with indicia providing data characterising each sample and correlated with each sample,

110 F. means for enabling plastic support with the samples and indicia thereon through apparatus which is adapted to allow examination of the samples for microscopical study and analysis,

115 G. means for recording the data of the examination results (from F) and correlating them with the indicia (from E),

H. means for processing and storing the correlated data (from G) to give and output of 120 the data relationship of examination data to

samples in selected report form.

25. Apparatus for the examination of a sequential series of samples comprising one or more of the features A to H specific in Claim 5 24 above, adapted to be used for assembly into an apparatus for operation of a method as claimed in any one of Claim 1 to 22.

26. Apparatus for the examination of a sequential series of samples substantially as described.

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